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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/935,100 | 08/22/2001 | David B. Weiner | UPN-4099 | 2243 |

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| EXAMINER | |
|---|---|
| PARKIN, JEFFREY S | |
| ART UNIT | PAPER NUMBER |
| 1648 | |

DATE MAILED: 06/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/935,100 | WEINER ET AL. | |
| | Examiner | Art Unit | |
| | Jeffrey S. Parkin, Ph.D. | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 03 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *4/6/2006; 5/3/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *32-34,36-38,40,41,43,44 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-34, 36-38, 40, 41, 43, 44, and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

**Response to Amendment**

***37 C.F.R. § 1.114***

A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114.

***Status of the Claims***

Claims 32-34, 36-38, 40, 41, 43, 44, and 46 are currently under examination.

***35 U.S.C. § 103(a)***

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the

various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 32, 36, 37, 38, and 40 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Sato *et al.* (199) in view of Matsushita (1998). Sato and colleagues provide polyclonal antibodies that are reactive with amino terminus of human immunodeficiency virus type 1 (HIV-1) viral protein R (Vpr). This teaching does not discuss the production of monoclonal antibodies (Mabs) or the preparation of pharmaceutical compositions comprising these antibodies. However, Matsushita provides pharmaceutical compositions comprising gp120-specific monoclonal antibodies. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare pharmaceutical compositions, as taught by Matsushita, comprising the anti-Vpr antibodies provided by Sato and colleagues. One of ordinary skill in the art would have been motivated to prepare sterile solutions containing anti-Vpr antibodies and to include pharmaceutically acceptable carriers because this would increase the stability and shelf-life of the product. It would have also been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare anti-Vpr Mabs using the methods of Matsushita and the immunogens of Sato and colleagues, since this would provide a high-affinity

immunological reagent useful for diagnostic and other applications.

### *35 U.S.C. § 112, First Paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

*Enablement*

Claims 33, 34, 41, 43, 44, and 46 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed toward a method of treating individuals exposed to or infected with HIV by administering anti-Vpr antibodies. The disclosure (see p. 65) clearly states that "anti-vpr antibodies may be administered as **therapeutics** to **treat individuals infected** with HIV. The anti-vpr [sic-Vpr] antibodies are preferably produced against eukaryotically-produced vpr [sic-Vpr]. They are administered in an effective dose; i.e. a dose sufficient to inactivate some or all of the vpr [sic-Vpr] present in the individual such that the progress of HIV in the individual is inhibited or otherwise reduced. Multiple doses may be administered." Thus, to practice the claimed invention, the skilled artisan would require a composition comprising a high-affinity antibody or antibodies with the desired pharmacological profile.

As previously set forth, the legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

*Inadequate Direction/Guidance Provided*

**The disclosure fails to provide adequate guidance pertaining to the structural and functional characteristics of the anti-Vpr antibodies present in the pharmaceutical composition.** The specification is silent pertaining to the epitope(s) recognized, the affinity of the antibody composition, the avidity of the antibody composition, and the pharmacological properties (i.e., serum half-life, bioavailability, clearance rate, sequestration by serum proteins, target distribution, target levels, etc.) (Gait and Karn, 1995). The skilled artisan would require a knowledge of these various properties before attempting to administer the antibody composition to a patient. Moreover, Vpr is a regulatory protein that may not be readily accessible to circulating antibodies. Thus, even if applicants were able to identify a high-affinity antibody, it is not readily manifest

that said antibody would have the requisite neutralizing activity to be effective as a therapeutic.

**The disclosure fails to provide adequate guidance pertaining to the role of extracellular versus intracellular Vpr in HIV pathogenesis and disease progression.** The claimed invention appears to be predicated upon the finding that polyclonal anti-Vpr antisera can neutralize extracellular Vpr *in vitro*. However, the relevance of this finding to the clinical sequelae associated with disease progression remains to be elucidated. Thus, it is not readily manifest to the skilled artisan if extracellular Vpr plays a significant role in this process. Moreover, considering the large amounts of virus and viral antigens that are produced during viral replication (~2 X $10^9$ virions/day; Ho *et al.*, 1995), it is not readily apparent that a sufficient titer of anti-Vpr antibody can be maintained to sufficiently neutralize Vpr and its attendant activities. It is also not readily manifest if anti-Vpr antibodies can be efficiently targeted to the various compartments where HIV replicates for a sufficient period of time to exert a meaningful clinical effect. Additional experimentation is required to address these concerns.

*Claim Breadth is Excessive*

**The claims are broadly directed toward any population of anti-Vpr antibodies.** Thus, they may include specific monoclonal reagents (none of which are described in the specification), polyclonal reagents, or recombinant antibodies. The claims do not specify any type of neutralizing activity or other properties for the antibodies. In order to practice the claimed invention the skilled artisan would need a purified, well-characterized reagent (i.e., a Mab produced from a specific hybridoma). However, the specification is silent pertaining the properties of any given antibody composition.

*State-of-the-Art*

**The state-of-the-art vis-à-vis the treatment of HIV infection using immunotherapeutics can be characterized by unpredictability and frequent failure.** Applicants propose to treat HIV-infected patients by administering compositions comprising anti-Vpr antibodies that will presumably negate the activities of extracellular Vpr. Immunotherapeutic approaches to treating HIV infection have not been terribly successful. Lindhardt *et al.* (1989) reported that high avidity antibodies to one of the structural proteins were present during disease development in the patient population examined. Thus, the presence of these antibodies did not appear to have any influence on disease progression. Thus, the skilled artisan, even if armed with a highly specific neutralizing reagent, cannot predict if that reagent will have a meaningful clinical outcome. Each antibody composition must be tested empirically, preferably in a human host since most animal models are inadequate and do not allow the direct extrapolation of findings from one system to another. Moreover, some passive immunotherapy studies have reported that there was no clinical benefit in HIV-infected patients receiving Ig preparations (Jacobson *et al.*, 1993). Karwowska et al. (1991) also examined the effectiveness of immunotherapeutics for the treatment of HIV infection and concluded that "Whether such MAb cocktails will be effective in the prophylaxis or treatment of HIV infection will be determined only by clinical trials." This is not surprising considering all the uncertainty associated with attempting to identify the correlates of protective immunity and the ability of the virus to direct the immune response predominantly toward low affinity antibody responses (Kohler et al., 1992).

*Absence of Working Embodiments*

The disclosure fails to provide any working embodiments demonstrating the HIV-1 or -2 Vpr-specific antisera are effective at combating HIV infection. Considering the unpredictability of the art and nature of the invention, the skilled artisan would clearly require suitable working examples before contemplating practicing the invention on an infected patient.

When all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation to practice the claimed invention.

*Response to Arguments*

Applicants' traverse and submit that the invention is fully enabled. A declaration was provided by Dr. David B Weiner under 37 C.F.R. § 1.132 asserting that HIV-1 Vpr exists in an extracellular capacity and can be neutralized *in vitro* utilizing a polyclonal rabbit antisera. The examiner does not dispute these findings. However, they are insufficient to overcome the rejection for a number of reasons. First, this experiment was performed in a simple *in vitro* tissue culture assay which does not address the role of extracellular Vpr in HIV pathogenesis. This assay did not measure extracellular Vpr levels in infected patients, demonstrate that these quantities are biologically significant, and that said protein can be effectively neutralized by anti-Vpr antisera. Second, the data provided in the declaration is insufficent to enable the full breadth of the claimed invention. The antisera employed were obtained from rabbits and were directed toward a different epitope than that set forth in the specification. Moreover, there was no detailed discussion concerning the antibody properties (i.e., affinity, avidity, isotype, etc.) that contributed to the alleged positive effect. Thus, the skilled artisan cannot reasonably predict,

based upon this study, which antibodies will reasonably be effective in an *in vivo* setting. Applicants' additional arguments have also been considered but are deemed to be nonpersuasive for the reasons set forth *supra*.

Additional Prior Art

The following prior art, which was not relied upon in the office action, is considered germane to applicant's disclosure:
-Garrett, E. D., *et al.*, 1991, Rev activates expression of the human immunodeficiency virus type 1 *vif* and *vpr* gene products, J. Virol. 65(3):1653-1657.

***Correspondence***

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Bruce R. Campell, Ph.D., can be reached at (571) 272-0974. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

25 June, 2006